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In This Issue

Zonisamide (Zonegran®): A Brief Review

Indications

Zonisamide is indicated for use as adjunctive therapy in the treatment of partial seizures in adults with epilepsy (see Table 1).[1] Zonisamide may also be effective in the treatment of generalized tonic-clonic seizures, tonic seizures, atypical absence seizures, simple/complex partial seizures and secondary generalized tonic-clonic seizures, progressive myoclonus epilepsy, and infantile spasms.[2-7]

Table 1: Comparison of Indications for Newer FDA-Approved Adjunctive Antiepileptic Agents[1,8-11]

Seizure Type	Lamotrigine (*Lamictal & Lamictal CD*)	Levetiracetam (*Keppra*)	Tiagabine (*Gabitril*)	Topiramate (*Topamax*)	Zonisamide (*Zonegran*)
Adults					
Partial	X	X	X	X	X
Children					
Partial			X [a]	X[b]	
Lennox-Gastaut	X[b]				

a = children 12 years of age and older; b = children 2 years of age and older

Clinical Pharmacology

Zonisamide is a sulfonamide anticonvulsant, structurally unrelated to other antiepileptic agents.[1,12] In animal models, zonisamide can inhibit experimental seizures, electroshock- or pentylenetetrazol-induced maximal seizures and kindled seizures.[13,14] However, it does not inhibit the minimal seizures evoked by pentylenetetrazol.[13,14] Zonisamide's anticonvulsant action is probably the result of its blocking neuronal calcium T-channel and sodium channel activity and not the modulation of gamma aminobutyric acid (GABA) or carbonic anhydrase (see Table 2).[12-17] Its effects on sodium and calcium channels stabilize neuronal membranes and suppress neuronal hypersynchronization.[1] Zonisamide also facilitates dopaminergic and serotonergic neurotransmission, but the importance of these effects on the antiepileptic activity of the drug is unknown.[1,18] However, the effects on the dopaminergic system may explain why resting and postural hand tremors have been reported by some patients and why patients with bipolar mania, schizoaffective mania, and schizophrenic excitement may improve with zonisamide therapy.[18] Zonisamide is also a weak carbonic anhydrase inhibitor; however, this effect is not thought to contribute to its anticonvulsant activity.[1,17]

The effects of zonisamide in global cerebral ischemia are also being evaluated. The animal data indicate that zonisamide may have antihypoxic effects and may decrease hypoxic-ischemic brain damage secondary to transient focal ischemia or stroke.[13] This activity appears to be related to zonisamide's effectiveness on voltage-dependent calcium T-channels and its ability to scavenge radicals and inhibit lipid peroxidation.[13]

Pharmacokinetics

Zonisamide is rapidly absorbed following oral administration. Peak serum concentrations occur within 2-6 hours of administration. Administration with food has no effect on the extent of oral absorption; however, the time to maximum concentration is delayed to

Table 2: Comparison of the Mechanism of Action of Selected Newer Anticonvulsants[1,8,-12,14,19-22]

Drug	Chemical Name	Mechanism of Action
Lamotrigine	6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine	Inhibits presynaptic voltage-dependent sodium channels, resulting in decreased release of excitatory amino acids glutamate and aspartate
Levetiracetam	(-)-(S)-"-ethyl-2-oxo-1-pyrrolidine acetamide	Unknown
Tiagabine	(-)-R-1-[4,4-bis(3-methyl-2-thienyl)-3-butenyl]nipecotic acid	Centrally acting gamma aminobutyric acid (GABA) uptake inhibitor
Topiramate	2,3:4,5-bis-*O*-(1-methylethylidene)-$-D-fructopyranose sulfamate	Inhibition of sodium channels, augmentation of GABA activity, and antagonism of kainate activity
Zonisamide	1,2-benzisoxazole-3-methanesulfonamide	Inhibits calcium T-channels and sodium channel activity

4 to 6 hours. Animal data also suggest zonisamide may be well absorbed following rectal administration. The level of zonisamide is higher in erythrocytes than in plasma and may exceed plasma levels by 4- to 9-fold. Serum levels increase proportionately with dose over the 200 to 400 mg range; however, the peak concentration and AUC increase disproportionately at 800 mg, probably due to saturable binding of zonisamide to red blood cells. The therapeutic plasma range for zonisamide may be 7 to 40 mg/L with the target steady-state concentration being 20 mg/L.[1,14,17,20,23-26]

The volume of distribution of zonisamide is 1.2 to 1.8 L/kg.[1,12] In addition to the erythrocytes, zonisamide is also present in the liver, kidneys, and adrenal glands at concentrations twice that of the plasma.[17] Plasma protein binding is approximately 40%, principally to albumin. Zonisamide is metabolized by the microsomal cytochrome P450 isozyme (primarily 3A4, but to a lesser extent maybe also 3A5, 2C19, and 2D6) in the liver to 2-sulfamoylacetyl phenol (SMAP).[1,12] Administration of anti-P450 3A4 antibodies results in decreased zonisamide clearance, while anti-P450 2D6 antibodies had no effect *in vitro*. Zonisamide is also excreted unchanged in the urine (30% to 50%). The plasma elimination half-life is 63 hours (see Table 3). The elimination half-life of zonisamide in red blood cells is about 105 hours.[1,14,20,23,24] The half-life of zonisamide is reduced to 27 to 46 hours when it is administered with enzyme-inducing anticonvulsants.[1,12]

Zonisamide renal clearance declines with decreasing renal function. In patients with a creatinine clearance less than 20 mL/min, the zonisamide AUC was increased 35%. Slower dosage titration should be considered in patients with impaired renal function.[1] The pharmacokinetics of zonisamide have not been evaluated in patients with hepatic dysfunction, but a slower dosage titration should also be done in this population until more information on the impact of hepatic dysfunction on zonisamide clearance is determined.[1] The pharmacokinetics of zonisamide appear to be similar in the young and elderly.[1] Serum levels of zonisamide in children are lower than in adults receiving comparable mg/kg doses due to increased clearance.[27]

The pharmacokinetic properties of some of the antiepileptic agents (eg, valproic acid, zonisamide) were altered the day of brain surgery. There is an increase in total clearance and renal clearance and an increase in volume of distribution with zonisamide, and the zonisamide concentration was increased in erythrocytes the day of the procedure.[23]

Comparative Efficacy

The majority of studies evaluating zonisamide in the treatment of adult complex seizures were conducted in Japan. The original publications are in Japanese or abstract form and are not readily available. The results of these studies were summarized in several other papers[3,14,17] and are included in Table 4. Zonisamide was also useful in the treatment of generalized tonic-clonic seizures, tonic seizures, atypical absence seizures, simple/complex partial seizures and secondary generalized tonic-clonic seizures, progressive myoclonus epilepsy, and infantile spasms.[3-7,14,17,26] Preliminary data also suggest zonisamide may have neuroprotective and antimanic activity.[26]

An open-label study conducted in the United States used historical controls to determine the short-term effectiveness and long-term safety of zonisamide therapy. The zonisamide therapy was started in 167 patients with refractory partial seizures. The patient's pre-zonisamide treatment seizure level while receiving one to two antiepileptic drugs was used as the control period. The zonisamide was then added to the antiepileptic drug regimen, and the dose was titrated over 4 weeks and continued for another 12 weeks. The patients were then allowed to enter the long-term safety portion of the study. The starting dose of zonisamide was 50 mg or 1.5 mg/kg, whichever was larger. The dose was adjusted at weekly intervals during the first 4 weeks and could range from 50 to 1100 mg/day. At the end of 16 weeks, 50% were treated with 400 to 500 mg/day, and the median final dose was 500 mg/day. The median number of seizures at baseline was 11.5 per month. The seizure rate decreased to 7.4 per month during the entire evaluative period and had decreased to 5.5 per month during the last month. A 50% or greater reduction in complex partial seizures occurred in 43.2%, and 9.2% had no seizures after 3 months of zonisamide therapy. Zonisamide was also effective in those patients in whom partial seizures had become generalized. During the long-term safety portion of the study, the majority of

Table 3: Comparison of Pharmacokinetic Parameters for Newer Anticonvulsants[1,3,8-12,14,19-24,27-29]

Pharmacokinetic Parameter	Lamotrigine	Levetiracetam	Tiagabine	Topiramate	Zonisamide
Bioavailability (F)	98%	100%	90%	80%	≥50%
Time to Peak (Tmax)	1.4-4.8 hr	na	0.5-1.5 hr	2 hr	2-6 hr
Protein binding (PB)	55%	<10%	96%	13-17%	40%
Volume of distribution	0.9-1.3 L/kg	na	1.1-1.3 L/kg	na	1.2-1.8 L/kg
Half-life (T _)	12.6-58 hr	7 h	5.4-9 hr	18-24 hr	63 hr
Hepatic elimination	Glucuronidation	hydrolysis	microsomal cytochrome P-450 (3A); enterohepatic recycling	hydroxylation, hydrolysis, and glucuronidation	microsomal cytochrome P-450 (3A4)
Active metabolite	no	no	no	no	no
Fraction excreted unchanged in the urine (fe)	10%	66%	2%	70%	30-50%
Food	no effect	delays Cpmax	delays Cpmax	no effect	delays Cpmax
Enzyme inducer	no*	no	no	no	no
Enzyme inhibitor	no	no	no	inhibits the activity of CYP2C19	

* = may cause autoinduction when used as monotherapy; na = not available

adverse effects were mild or moderate and occurred more frequently during the first month of therapy.[25]

The product labeling includes a summary of three multicenter, placebo controlled, double-blind, 3-month clinical trials completed in the U.S. and Europe that enrolled 499 patients with refractory partial onset seizures with or without secondary generalization. Participating patients had a history of at least 4 partial onset seizures per month despite therapy with one or more antiepileptic agents at therapeutic concentrations. Zonisamide or placebo was added to existing therapy. In the first study enrolling 203 patients, zonisamide was administered in one of two dose-escalation regimens: 100 mg/day for 5 weeks, 200 mg/day for 1 week, 300 mg/day for 1 week, then 400 mg/day for 5 weeks; or 100 mg/day for 1 week, 200 mg/day for 5 weeks, 300 mg/day for 1 week, then 400 mg/d for 5 weeks. The total daily dose was divided into two doses. The median reduction in partial seizures during weeks 8 through 12 was 40.5% in the zonisamide group compared to 9% in the placebo group ($p<0.05$). A 50% or greater reduction in seizure frequency was achieved in 41.8% of zonisamide-treated patients compared to 22.2% of placebo-treated patients ($p<0.05$).[1]

In the other two studies, zonisamide was dosed as 100 mg/day for 1 week, 200 mg/day for 1 week, then 400 mg/day for 2 weeks, after which the dose could be adjusted to a maximum dose of 20 mg/kg/day or a maximum plasma level of 40 mcg/mL. Doses were divided twice daily in the second study and given as a single daily dose in the third study. In the second study, the average final maintenance dose was 530 mg/day. The median reduction in partial seizures during weeks 5 through 12 in the second study was 29.6% in the zonisamide group compared to an increase of 3.2% in the placebo group ($p<0.05$). A 50% or greater reduction in seizure frequency was achieved in 29% of zonisamide-treated patients compared to 15% of placebo-treated patients.[1] The final average maintenance dose was 430 mg/day in the third study. The median reduction in partial seizures during weeks 5 through 12 was 27.2% in the zonisamide group compared to an increase of 1.1% in the placebo group ($p<0.05$). A 50% or greater reduction in seizure frequency was achieved in 28% of zonisamide-treated patients compared to 12% of placebo-treated patients ($p<0.05$).[1] In the third study, the median seizure rate dropped from 12 per month to 7.1 per month in the group treated with zonisamide, and no change (8.8 per month) was noted in the group treated with placebo. No seizures were reported in 6.2% of the zonisamide group.[30]

The long-term safety and efficacy of zonisamide were evaluated in 115 children treated for more than 1 year. All of the children had generalized or partial epilepsy. Sixty six had intellectual disability and 49 were of normal intelligence. Zonisamide monotherapy was administered to 28 children, 6 with intellectual disability and 22 with normal intelligence. The other children received polytherapy. The mean number of concomitant antiepileptic agents was 4.5 for the children with intellectual disability and 3 for the children with normal intelligence. A greater than 50% reduction in the number of seizures was achieved in 41% of the children with

Table 4: Summary of Zonisamide Clinical Trials

Type of Patients	Drug Regimen	# Pts	Duration	Study Design	Results	Ref
Uncontrolled epilepsy with 1 to 3 antiepileptic drugs or not previously treated	Zonisamide 330 mg/day Carbamazepine 600 mg/day	123	16 weeks	DB	The average frequency of simple/complex partial seizures per 4 weeks decreased from 14.9 to 3.5 with zonisamide and 13.3 to 4.4 with carbamazepine; the number of secondarily generalized tonic-clonic seizures decreased from 1.8 to 0.6 and 2.1 to 0.7, respectively. A >50% reduction in seizure frequency from baseline was achieved in 82% treated with zonisamide and 71% with carbamazepine. Overall, improvement rate was 66% with zonisamide and 65% with carbamazepine. Incidence of side effects was 52% with zonisamide and 57% with carbamazepine.	14,3,17
Pediatric patients with convulsive and non-convulsive generalized seizures	Zonisamide 7.3 mg/kg/day Valproic acid 27.6 mg/kg/day	32	8 weeks		≥50% reduction in seizures occurred in 77% with zonisamide and 53% with valproic acid. Overall improvement rating was 50% with zonisamide and 44% with valproic acid.	14,3
Pediatric and adult patients with partial, generalized and mixed seizure types	Zonisamide 5.9-8.8 mg/kg/day & Cp 19.6-20.7 mg/L	1008	253 day average	OL	Overall improvement rate was 56%. Improvement rates were 61% in simple partial seizures, 52% in complex partial seizures, 61% in secondary generalized tonic-clonic seizures, 53% in generalized tonic-clonic seizures, 35% in generalized tonic seizures, 73% in atypical absence seizures, 30% in atonic seizures, 29% in myoclonus seizures, and 54% in the mixed generalized seizures in the add-on treatment group in patients previously uncontrolled with other agents. The values for the monotherapy with zonisamide are even better.	14,3,26
Refractory partial seizures including secondary generalization	Zonisamide 100 to 1,000 mg/day Placebo	139	12 weeks	DBPC	Overall improvement was 62% with zonisamide and 19% with placebo. Seizure frequency decreased by 28% with zonisamide and increased by 4% with placebo. ≥50% reduction in seizures occurred in 30% with zonisamide and 19% with placebo.	14,3,17
Refractory partial seizures including secondary generalization	Zonisamide median daily dose 6.7 to 7.2 mg/kg Placebo	152	12 weeks	DBPC	Reduction in seizure frequency of 30.1% in zonisamide group compared to a 0.3% increase in placebo group. >50% reduction in seizures occurred in 28.6% with zonisamide and 13.2% with placebo.	17
Refractory partial seizures	Zonisamide 50 to 1,100 mg/day plus other antiepileptic drugs	137	16 weeks	OL	≥50% reduction in seizures occurred in 41% of all patients with zonisamide, 43% of those with complex partial seizures and 68% of those with secondarily generalized tonic-clonic seizures.	14
Refractory complex partial seizures	Zonisamide plus other antiepileptic drugs	6	38-48 months	OL	Seizure control was variable throughout the study.	32
Refractory complex partial seizures	Zonisamide plus other antiepileptic drugs	167	16 weeks	OL	Median number of seizures decreased from 11.5 per month to 7.4 per month. ≥50% reduction in complex partial seizures occurred in 43.2% and 9.2% had no seizures.	25
Refractory partial seizures	Zonisamide 1.5-7 mg/kg Placebo	139	12 weeks	DBPC	Median seizure rate dropped from 12 per month to 7.1 per month with zonisamide and no change with placebo. ≥50% reduction in seizures in 29.9% with zonisamide and 9.4% with placebo. No seizures were reported in 6.2% with zonisamide.	30

DB = multicenter, double-blind; DBPC = multicenter, double-blind, placebo controlled; OL = open-labeled

intellectual disability and 67% of children with normal intelligence ($p<0.01$) during zonisamide therapy. Similar side effects were observed in the two groups, although side effects occurred more frequently in the children with intellectual disability receiving monotherapy (50%) than in the children with normal intelligence receiving monotherapy (27%). As has been observed with other antiepileptic agents, seizures in children with intellectual disability are less responsive to zonisamide therapy.[31]

Contradictions, Warnings, and Precautions

Zonisamide is contraindicated in patients with a history of hypersensitivity reactions to sulfonamides, zonisamide, or the ingredients of the capsule (microcrystalline cellulose, hydrogenated vegetable oil, sodium laurel sulfate, gelatin, and colorants).[1]

Severe reactions to sulfonamides can include Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Zonisamide should be immediately discontinued if signs of hypersensitivity or other serious reactions occur. If rash occurs, discontinuation of therapy should be considered. If zonisamide is not discontinued, the patient should be closely observed. Seven deaths from severe rash (Stevens-Johnson syndrome and toxic epidermal necrolysis) were reported during the first 11 years of marketing of zonisamide in Japan. A total of 49 cases of Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported during post-marketing experience in Japan, representing a reporting rate of 46 per million patient-years of exposure (0.000046%). It is believed this is probably an underestimate of the true incidence.[1] The incidence of rash requiring discontinuation of therapy has been approximately 2% in clinical trials. The rash does not appear to be dose related.[1]

Serious hematologic toxicities, including two cases of aplastic anemia and one case of agranulocytosis, were reported during the first 11 years of marketing of zonisamide in Japan. Two cases of agranulocytosis were also reported during clinical trials.[1]

Oligohydrosis and hyperthermia have been reported in pediatric patients treated with zonisamide. Because decreased sweating may be associated with elevated body temperature, especially during the summer, body temperature should be closely monitored.[1]

Zonisamide frequently causes central nervous system side effects, such as: 1) psychiatric symptoms, including depression and psychosis; 2) psychomotor slowing, difficulty with concentration and speech or language problems (especially word-finding difficulties); and 3) somnolence or fatigue. During clinical trials, zonisamide-treated patients more frequently required discontinuation of therapy due to depression, required hospitalization for depression or suicide attempts, and required discontinuation of therapy due to psychosis or psychosis-related symptoms compared to placebo-treated patients. Psychomotor slowing, difficulty concentrating, somnolence, and fatigue were most evident in the first month of therapy and were generally associated with doses above 300 mg/day. Speech and language problems tended to occur after 6 to 10 weeks of therapy and at doses above 300 mg/day.[1]

Kidney stones occurred in 4% of patients treated with zonisamide in clinical trials. Stones were typically composed of calcium or urate salts. Increasing fluid intake and urine output may reduce the risk of stone formation.[1] The earlier clinical trials with zonisamide were stopped because of the development of urinary caliculi in some patients.[3,14,25]

Because zonisamide is metabolized in the liver and eliminated by the kidneys, caution is recommended when administering zonisamide to patients with hepatic or renal impairment.[1] Use is not recommended in patients with renal failure (GFR < 50 mL/min).[1] In some clinical trials, an increase in serum creatinine and blood urea nitrogen was observed in zonisamide-treated patients. The effects persisted over time, but were not progressive. Acute renal failure did not occur during clinical trials. Therapy should be discontinued if acute renal failure occurs or a clinically important sustained increase in serum creatinine or blood urea nitrogen occurs.[1]

Liver damage was observed in dogs treated with zonisamide for 1 year. The clinical significance of these findings for humans is not known.[1]

As with other antiepileptic agents, abrupt discontinuation of zonisamide may cause an increase in seizure frequency or status epilepticus. Dose reduction or discontinuation should be done gradually.[1] Sudden unexplained deaths have occurred among patients treated with zonisamide; however, the rate has not exceeded that of sudden unexplained deaths in patients with refractory epilepsy not receiving zonisamide.[1]

The safety and effectiveness of zonisamide in pediatric patients have not been established. Zonisamide is not FDA approved for use in pediatric patients (<16 years). Oligohydrosis and hyperthermia have been reported in pediatric patients treated with zonisamide.[1]

Zonisamide is in Pregnancy Category C. It is a teratogen. In animal studies, zonisamide was teratogenic and embryolethal. A variety of external, visceral, and skeletal malformations were observed, including a number of cardiovascular defects. Zonisamide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.[1] Because of the potential for severe adverse effects in nursing infants, it is recommended that either nursing be discontinued or zonisamide be discontinued.[1] Zonisamide can cause abortion and fetal malformation in laboratory animals.[2] Preliminary information on the teratogenic effects of zonisamide in humans indicates the risks associated with its use during pregnancy are similar to other antiepileptic drugs. Malformations have been reported in two cases where the mother was taking multiple antiepileptic drugs, and no problems were reported in four mothers who were taking zonisamide as monotherapy.[33] Nursing is not recommended because zonisamide has been found in animal milk.[2] The FDA has urged the manufacturer to create and maintain a pregnancy registry.[34]

Adverse Reactions

The most common side effects reported in the clinical trials have included drowsiness, ataxia, dizziness, loss of appetite, weight loss, nausea, slowing of mental activity, depression, and agitation/irritability.[1,2,12,14,25,30,32,35] Other potential adverse effects associated with zonisamide therapy are diarrhea, dyspepsia, dry mouth, blurred vision, diplopia, nystagmus, ocular pain, nervousness, headache, unusual taste, rash, asthenia, confusion, speech abnormalities, dysarthria, tremor, paresthesia, fever, leukopenia, anemia, elevations in liver function test, abnormal thinking, and behavior disorder in children.[1,2,14,30,32,36]

In one analysis based on the results from several clinical trials, withdrawal of therapy due to side effects appeared to occur more frequently with zonisamide than other adjunctive antiepileptic agents (gabapentin, lamotrigine, tiagabine, topiramate).[35]

Drug Interactions

Zonisamide can increase serum carbamazepine levels as the dose of zonisamide is increased. The change in serum carbamazepine was more related to the change in zonisamide dose than zonisamide serum levels and was unrelated to changes in protein binding.[37] Others have reported reduced carbamazepine concentrations.[27] Carbamazepine may increase plasma and erythrocyte zonisamide concentrations.[14] The clearance of zonisamide is increased by phenobarbital, phenytoin, and carbamazepine, which would reflect the consequences of cytochrome P450 enzyme induction.[1,14] The half-life of zonisamide is reduced to 27 hours by phenytoin and to 38 hours by phenobarbital and carbamazepine, but remains largely unchanged at 46 hours by valproate.[1]

In *in vitro* studies, zonisamide metabolism was markedly inhibited by cyclosporine, dihydroergotamine, ketoconazole, itraconazole, miconazole, and triazolam.

Table 5: Comparison of Recommended Dosing Regimens for Newer Anticonvulsants[8-11,14,21,22,25]

Drug	Recommended Dose	Comments
Lamotrigine	Initial dose is 25 mg every other day for 2 weeks, followed by an increase to 25 mg daily for 2 weeks; 50 to 150 mg/day administered as a divided dose twice daily.	Due to the increased risk of rash, initial doses in patients also receiving valproic acid should not exceed 25 mg every other day. Patients on other antiepileptic medications, but not valproic acid, should be started on 50 mg once daily for 2 weeks followed by an increase to 50 mg twice daily for 2 weeks, with subsequent dosage adjustments up to 300 to 500 mg per day given in two doses.
Levetiracetam	Levetiracetam should be initiated at a dose of 100 mg/day, administered as a divided dose of 500 mg twice daily. The dose may be increased by 1000 mg/day every 2 weeks up to a maximum recommended dose of 3000 mg/day.	Dosage adjustments are necessary based on renal function. Adjusted dosages are required in patients with CrCl < 80 mL/min.
Tiagabine	Tiagabine should be initiated at a dose of 4 mg once daily. In adolescents 12 to 18 years of age, the daily dose may be increased by 4 mg at the beginning of week-2 and then increased by 4 to 8 mg weekly thereafter until a clinical response is achieved or up to 32 mg/day. In adults, the total daily dose may be increased by 4 to 8 m g at weekly intervals until clinical response is achieved or up to 56 mg/day.	Patients taking only non-enzyme-inducing antiepileptic agents (eg, valproate, gabapentin, lamotrigine) may require lower tiagabine doses and slower dose titration. Tiagabine should be administered in divided doses two to four times daily. Administration multiple times a day minimizes side effects associated with fluctuations in plasma drug concentrations. Tiagabine should be administered with food.
Topiramate	Therapy should be initiated with 50 mg/day and titrated to an effective dose. Recommended total daily dose is 400 mg in two divided doses. Doses higher than 1600 mg have not been studied.	In patients with renal impairment (creatinine clearance <70 mL/min/1.73 m^2), one-half the usual adult dosage is recommended.
Zonisamide	Therapy should be initiated at 100 mg/day and slowly titrated to an effective dose, allowing at least 2 weeks at each dosage level before subsequent dosage increases. Doses of 100 to 600 mg/day administered as a single-daily dose or in divided dose two times daily.	Slower dosage titration recommended in patients with renal or hepatic impairment.

Clinically important drug interactions are more likely to occur with ketoconazole, cyclosporine, miconazole, fluconazole, and carbamazepine than with dihydroergotamine, itraconazole, and triazolam.[38]

The protein binding of zonisamide is unaffected by carbamazepine, phenobarbital, and phenytoin. Therapy with valproic acid can make small increases in zonisamide free fraction. Zonisamide does not affect the protein binding of phenytoin, phenobarbital, or carbamazepine.[14]

Dosing

The initial dose is 100 mg once daily. After 2 weeks the dose can be increased to 200 mg/day and kept at that dose for at least 2 weeks. The dose can be further increased to 300 mg/day and 400 mg/day, with the dose held stable for at least 2 weeks to achieve steady state at each dosage level. Doses of 100 to 600 mg/day were effective, although no evidence of increased response was noted at doses above 400 mg/day. Experience with doses exceeding 600 mg/day is limited.[1] Therapy can be initiated more gradually at the prescribers discretion to allow additional time to assess efficacy at lower doses.[1]

Zonisamide can be administered once or twice daily, except for the 100 mg initial dose that is given once daily. It may be taken with or without food. The capsules should be swallowed whole.[1] The dose can be increased every 1 to 2 weeks up to a maximum of 600 mg/day.[2,14,25] See Table 5 for a comparison of the dosing recommendations for the newer antiepileptic agents.

Slower titration and more frequent monitoring is recommended in patients with renal or hepatic disease.[1]

Recommended Monitoring

Routine monitoring of plasma zonisamide levels is not recommended. In clinical trials, concentrations of 7 to 40 mcg/mL have been associated with a therapeutic response, and target levels of 10 to 40 mcg/mL have been advocated. Additional studies are necessary, however, to validate this therapeutic range. Levels exceeding 30 mcg/mL may be associated with increased adverse effects.[17,26,27,29] Periodic monitoring of renal function tests is recommended.[1] Consideration should also be given to monitoring hepatic function and complete blood counts.[2]

Product Availability

The investigational new drug application for zonisamide was filed in 1982 in the United States by Warner-Lambert. However, in 1987 Warner-Lambert decided to discontinue studying the drug and returned the licensing rights to Dainippon.[39] Zonisamide was approved for marketing in Japan in 1989 and was available from Dainippon under the trade name *Excegran*.[3,40,41]

Elan received an approvable letter for zonisamide from the U.S. Food and Drug Administration (FDA) on March 19, 1998. Final approval awaited additional assessment of adverse effects associated with zonisamide therapy and review of the post-marketing data from Japan.[42] Elan received FDA approval for zonisamide in March 2000. It is being marketed by Elan subsidiary Athena Neurosciences.[40,41]

Zonisamide is available as 100 mg capsules in bottles of 100.[1]

Cost

Refer to Table 6.

Patient Information

Patients taking zonisamide should be counseled as follows:

- Notify your physician before taking this medication if you are allergic to "sulfa" drugs like Bactrim or Septra
- Contact physician immediately if a rash develops or if seizures worsen
- Tell your doctor before stopping this or other seizure medications
- Tell your doctor if you are pregnant, nursing, or planning to become pregnant

Table 6: Comparative Prices of Various Antiepileptic Drugs

Antiepileptic Drug	Average Adult Daily Dose (mg)	Maximum Daily Dose (mg)	Monthly Cost Based on Average Daily Dose (FSS)*	Monthly Cost Based on Maximum Dose (FSS)	Monthly Cost Based on Average Daily Dose (AWP)**	Monthly Cost Based on Maximum Dose (AWP)
Lamotrigine (Lamictal®)	300	500	$65.81	$109.68	$132.53	$220.89
Levetiracetam (Keppra®)	1000	3000	$61.87	$185.62	$109.72	$329.17
Tiagabine (Gabitril®)	32	56	$78.29	$137.00	$151.80	$265.65
Topiramate (Topamax®)	200	1600	$127.31	$509.24	$240.60	$962.40
Zonisamide (Zonegran®)	100	400	$26.72	$106.88	$59.72	$238.90

*FSS = Federal Supply Schedule

**AWP = Average Wholesale Price

Average adult daily doses based on indication as adjunctive therapy in the treatment of partial seizures (USPDI, AHFS, *Drug Information Handbook*).

- You may take this medicine with or without food
- Drink 6-8 full glasses of water each day. This may help prevent kidney stones.
- This medicine can cause drowsiness and coordination problems. Do not drive or operate dangerous machinery until you know how this medication affects you
- Notify your physician if you develop any of the following signs or symptoms:
  - Sudden back pain, abdominal pain, or blood in your urine
  - Fever, sore throat, sores in your mouth, or easy bruising
  - Become depressed
  - Start having thoughts that are unusual for you
  - Become very drowsy, have difficulty concentrating, or have coordination problems
  - Develop speech or language problems

Conclusion

Zonisamide will be a useful adjunctive agent in the treatment of partial seizures in adults with epilepsy. Zonisamide should not be used as monotherapy; instead, the drug should only be added to an existing antiepileptic drug regimen.

References

1. Elan Pharmaceuticals. Package literature for *Zonegran.* 27 March 2000.
2. Japan Pharmaceutical, Medical & Dental Supply Exporters' Association. *Japan Pharmaceutical Reference: 1991-1992.* 2nd Edition. Tokyo; Tanaka Printing. 1991.
3. Seino M, et al. Zonisamide. *Epilepsy Res* 1991;(Suppl 3):169-74.
4. Suzuki Y, et al. Zonisamide monotherapy in newly diagnosed infantile spasms. *Epilepsia* 1997;38:1035-8.
5. Kyllerman M, et al. Zonisamide for progressive myoclonus epilepsy: Long-term observations in seven patients. *Epilepsy Res* 1998;29:109-14.
6. Wallace SJ. Myoclonus and epileps y in childhood: A review of treatment with valproate, ethosuximide, lamotrigine and zonisamide. *Epilepsy Res* 1998;29:147-54.
7. Henry TR, et al. Progressive myoclonus epilepsy treated with zonisamide. *Neurology* 1988;38:928-31.
8. Hebel SK, editor. Drug Facts and Comparisons: Loose-Leaf Edition. St. Louis, MO: Facts & Comparisons, Inc., 2000.
9. Ladig DE. Mosby's *GenRx 1999: The Complete Reference for Generic and Brand Drugs*, ed. 9. St. Louis, MO: Mosby, 1999.
10. *Physicians' Desk Reference*, ed. 54. Montvale, NJ: Medical Economics Company, Inc., 2000.
11. Abbott Laboratories. Package literature for *Gabitril.* September 1997.
12. Bialer M, et al. Progress report on new antiepileptic drugs: A summary of the fourth Eilat conference (EILAT IV). *Epilepsy Res* 1999;34:1-41.
13. Minato H, et al. Protective effect of zonisamide, an antiepileptic drug, against transient focal cerebral ischemia with middle cerebral artery occlusion-reperfusion in rats. *Epilepsia* 1997;38:975-80.
14. Peters DH, Sorkin EM. Zonisamide: A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in epilepsy. *Drugs* 1993;45:760-87.
15. Masuda Y, et al. Evidence against a significant implication of carbonic anhydrase inhibitory activity of zonisamide in its anticonvulsive effects. *Arzneim-Forsch/Drug Res* 1994;44:267-9.
16. Masuda Y, Karasawa T. Inhibitory effect of zonisamide on human carbonic anhydrase *in vitro. Arzeim-Forsch/ Drug Res* 1993;43:416-7.
17. Leppik IE. Zonisamide. *Epilepsia* 1999;40(Suppl 5):S23-9.
18. Okada M, et al. Effects of zonisamide on dopaminergic system. *Epilepsy Res* 1995;22:193-205.
19. Britton JW, So EL. New antiepileptic drugs: Prospects for the future. *J Epilepsy* 1995;8:267-81.
20. Stiff DD, et al. Reductive metabolism of the anticonvulsant agent zonisamide, a 1,2-benzisoxazole derivative. *Xenobiotica* 1992;22:1-11.
21. Cada DJ (ed), Levien TL, Baker DE. Drug Evaluation - Tiagabine. In: *The Formulary Monograph Service* Dana Point, CA: December 1997.
22. UCB Pharma. Package literature for *Keppra.* 1 December 1999.

23. Ieiri I, et al. Pharmacokinetic study of zonisamide in patients undergoing brain surgery. *J Pharm Pharmacol* 1996;48:1270-5.

24. Nakasa H, et al. Characterization of human liver microsomal cytochrome P450 involved in the reductive metabolism of zonisamide. *Molecular Pharmacol* 1993;44:216-21.

25. Leppik IE, et al. Efficacy and safety of zonisamide: Results of a multicenter study. *Epilepsy Res* 1993;14:165-73.

26. Oommen KJ, Mathews S. Zonisamide: A new antiepileptic drug. *Clin Neuropharmacol* 1999;22:192-200.

27. Perucca E. The clinical pharmacokinetics of the new antiepileptic drugs. *Epilepsia* 1999;40(Suppl 9):S7-13.

28. Kochak GM, et al. Steady-state pharmacokinetics of zonisamide, an antiepileptic agent for treatment of refractory complex partial seizures. *J Clin Pharmacol* 1998;38:166-71.

29. Tomson T, Johannessen SI. Therapeutic monitoring of the new antiepileptic drugs. *Eur J Clin Pharmacol* 2000; 55:697-705.

30. Schmidt D, et al. Zonisamide for add-on treatment of refractory partial epilepsy: A European double-blind trial. *Epilepsy Res* 1993;15:67-73.

31. Iinuma K, et al. Long-term effects of zonisamide in the treatment of epilepsy in children with intellectual disability. *J Intellect Disabil Res* 1998;42(Suppl 1):68-73.

32. Shimizu A, et al. Effects and side effects of zonisamide during long-term medication. *Curr Ther Res* 1990;47:696-706.

33. Kondo T, et al. Preliminary report on teratogenic effects of zonisamide in the offspring of treated women with epilepsy. *Epilepsia* 1996;37:1242-4.

34. Temple R. Approval letter for NDA 20-789. Food and Drug Administration. Department of Health and Human Services. 27 March 2000.

35. Marson AG, et al. The new antiepileptic drugs: A systemic review of their efficacy and tolerability. *Epilepsia* 1997; 38:859-80.

36. Kimura S. Zonisamide-induced behavior disorder in two children. *Epilepsia* 1994;35:403-5.

37. Minami T, et al. Influence of additional therapy with zonisamide (*Excegran*) on protein binding and metabolism of carbamazepine. *Epilepsia* 1994;35:1023-5.

38. Nakasa H, et al. Prediction of drug-drug interactions of zonisamide metabolism in humans from in vitro data. *Eur J Clin Pharmacol* 1998;54:177-83.

39. Anonymous. Trade and government memos. *The Pink Sheet* 1992;54(26):T&G-5.

40. Anonymous. Pharmaceutical product news. *Health News Daily* 1998;10(57):8.

41. Anonymous. FDA grants approvable status for Elan's *Zonegram*™. *PRNewswire* 24 March 1998.

42. Anonymous. The news this week. *The Pink Sheet* 1998;60(14):33.

Cada D (Ed), Baker D, Levien T. Zonisamide. The Formulary Monograph Service, Facts and Comparisons, October, 2001.

Drug Shortages

By Robert DeChristoforo, M.S.

All too common recently has been the problem of drug shortages. In some cases the shortage causes a minor inconvenience, and in other cases, the shortage causes a significant problem. According to the FDA, a drug shortage can occur when the total supply of all versions of the approved product available at the market level will not meet the current demand, or a registered manufacturer will not meet the current and/or projected demands for the potentially medically necessary use(s) at the user level. The FDA goes on to further state that some of the reasons for shortages include manufacturer and bulk supplier problems, active ingredient shortages, natural disasters, FDA enforcement actions, and corporate decisions to discontinue drugs.

One of the many frustrating issues about drug shortages is the lack of information surrounding the shortage itself. Many times the Pharmacy's first hint that there is a problem is a repeated "back order" of a pharmaceutical. Pharmacy's procurement section scrambles to find an alternative manufacturer or substitute. Changes however can lead to errors, especially when similar packaging contains a different concentration or strength of a product. Once it is fairly well known that there is a drug shortage, health systems are trying to purchase whatever they can. Hospitals try to borrow from each other, without compounding existing shortages. In many cases it's unclear when the shortage will be resolved. Pharmaceutical manufacturers (in my personal experience) are either reluctant to give out the full information, or it's difficult to reach someone who knows the real story. Does a manufacturer really want to disclose that they are under some type of FDA enforcement action? Do they want to publicly state that it was a corporate (economic) decision to discontinue the manufacture of a drug product? To some manufacturers' credit, a product removed from the market may still be available to certain patients through a special distribution program.

One example of a continuing drug shortage due to high demand is etanercept. The manufacturer has set up a special patient registration distribution program to ensure that patients who have begun treatment will have continued access to the drug. Prochlorperazine injection has been unavailable for months. The manufacturer of the generic product who had the major market share has been unable to supply it, possibly because of an FDA enforcement action. The innovator company that had continued to produce the branded product while the generic version was also marketed, no longer manufactures it. Corporate decision? Competition with another of its own branded anti-emetics?

Indomethacin suppositories, commonly used by NCI's Surgery Branch to combat the side effects of IL-2 therapy suddenly became unavailable. First we were told it would be available soon, and then we were informed it would no longer be available. After a short period of unavailability, the Pharmacy's Pharmaceutical Development Section was able to procure bulk indomethacin and manufacture indomethacin suppositories. Within a few months, a call from an influential official to the manufacturer, resulted in a call to the Clinical Center Pharmacy informing us that a large supply of the suppositories had been located and how much did we want to buy? We purchased a 2-year supply which we determined would be used within the expiration dating of the product.

What are some of the other shortages that currently exist? A partial list of shortages includes ganciclovir, furosemide, phenobarbital injection, piperacillin, hyaluronidase, caspofungin, prochlorperazine, Zosyn (piperacillin and tazobactam), tetanus toxoid, and peginterferon alfa-2b. Dexamethasone, isoproterenol, and intravenous immunoglobulin (IVIG) are three of the medication shortages that have been resolved.

The Pharmacy Department works to minimize shortages, but will inform prescribers when possible either through the clinical pharmacy specialists, e-mail, P&T actions, or messages in MIS. When a shortage will cause a major problem, prescribers who commonly use the drug are notified directly.

Want to know more about drug shortages or receive e-mails notifications of drug products added to FDA's Current Drug Shortages? Go to *http://www.fda.gov/cder/drug/shortages/* or call Pharmacy's Procurement Section at 301-496-9358.

FDA Safety Alerts

- You can access the latest safety information from the Food and Drug Administration website. To access "Dear Health Professional" letters, other safety notifications, and labeling changes related to drug safety, just point your browser to *www.fda.gov* and click on "MedWatch." MedWatch is the FDA's medical products reporting program.
- You can receive immediate e-mail notification of new material as soon as it is posted on the MedWatch website. Just send a subscription message to *fdalists@archie.fda.gov.* In the message body enter: *subscribe medwatch* and your e-mail address.

Formulary Update

The Pharmacy and Therapeutics Committee recently approved the following formulary changes:

Additions

Zonisamide (Zonegran), an oral antiepileptic
Verteporfin (Visudyne), an injectable agent for photodynamic therapy
Oxandrolone (Oxandrin), an oral androgen
Zoledronic Acid (Zometa), an injectable bisphosphonate
Cevimeline (Evoxac), an oral cholinergic agonist
Bicalutamide (Casodex), an oral nonsteroidal antiandrogen

Deletions

Ophthalgan Eye Drops
Tri-Vi-Sol
Tolazamide Tablets
Griseofulvin 250 mg Tablets
Histoplasmin Injection
Potassium Gluconate Elixir
Aminosalicylic Acid

Drug Information Service

- Patient-specific pharmacotherapy evaluation and management
- Comprehensive information about medications, biologics, and nutrients
- Critical evaluation of drug therapy literature
- Assistance with study design and protocol development
- Clinical trial drug safety monitoring
- Investigational drug information
- Parenteral nutrition assessment and management

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